American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Reply To:
Department of Federal Affairs
American Academy of Pediatrics
The Homer Building
601 Thirteenth Street, NW
Suite 400 North
Washington, DC 20005
202/347-8600
800/336-5475
Fax: 202/393-6137
E-mail: kids1st@aap.org
http //www.aap.org

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Request for Comment on First Amendment Issues [Docket No. 02N-0209]

Dear Sir/Madam:

The American Academy of Pediatrics (AAP), representing 57,000 pediatricians, is eager to respond to your request for comments on First Amendment issues. The questions posed by the Food and Drug Administration (FDA) are concerning to the AAP, particularly in light of ongoing legislative and regulatory efforts to increase the quality and quantity of properly studied and labeled medications for infants, children and adolescents. There is a long and occasionally tragic history related to achieving appropriate therapeutic protections for children and the public at large. A century of legislative and regulatory action focusing on protecting public health have led us to the following conclusions:

It is essential that the FDA regulate commercial promotion ("speech") of medical products when this is necessary to protect the public health. AAP believes there is no more compelling case to illustrate the need for placing some restrictions on commercial speech than in the case of infants, children and adolescents – this nation's most vulnerable population. Children require special vigilance by those in regulatory roles to continue current progress to protect them from the extrapolation of adult treatments without adequate, well-controlled studies in the pediatric population. Lack of informed pediatric labeling on drugs used in children, insufficient pediatric studies to allow such proper labeling, the history of disasters from using adult drugs in children (such as chlorampenicol and others) that result from the dynamic processes of child development and growth are only some of the reasons the FDA must limit the unproven promotion and advertising of drugs.

To open up the area of advertising to claims that do not have FDA scientific review jeopardizes public health and returns us to the patent medicine promotions of the turn of the last century and the therapeutic misadventures in children that in fact created the need for FDA itself.

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The Congress and the Administration have the responsibility and authority for protecting the public health of the nation. For almost 100 years the federal government has served as the watchdog over the pharmaceutical industry in an effort to ensure that the products used by the American public were safe and effective and to ensure that therapeutic claims, including those made through advertising and promotion, are truthful and accurate. Neither the executive nor the legislative branch should relax these protections.

Without the rigors of FDA's scientific drug approval process providing medications for children is in effect, a national experiment but one without any informed consent or scientific stringency. AAP provided testimony to the Senate Health, Education, Labor and Pensions Committee on April 23, 2002 addressing the issue of Human Subject Protections, as it related to the pediatric population. The issue of ensuring adequate and well-controlled study of drugs prior to marketing and promotion of a drug relates directly to the issue of human subject protection. Through the important clinical studies required by FDA, information is generated and then disseminated for use by pediatricians and other health professionals. The alternative to including children in these well-controlled, scientifically-valid pediatric studies is having hundreds of thousands of children taking medications in office settings or at home that have not been properly studied but which can and will be promoted for such use for commercial gain. Subjecting children to daily uncontrolled, unregulated, and unreported experiments versus including a significantly smaller number of children (thousands vs. hundreds of thousands) in controlled clinical research studies is a much-preferred and ethically appropriate alternative.

Should FDA interpret the outcome of the Supreme Court's decision on Thompson v. Western States Medical Center to allow marketing and promotion of unapproved (off-label) uses of drugs, they would be relegating children once again to a standard of care that values risks and profits over science. This would destroy the scientific underpinnings of the protection of public health that Congress has affirmatively legislated that the FDA provide.

Disseminating partial or unapproved information about drug use (e.g., off-label uses) through advertisements or promotions can be detrimental or life-threatening to children. It is only in the last four years, since the enactment of the pediatric provision (section 111) of the Food and Drug Administration Modernization Act (FDAMA -P.L. 105-115) and the 1998 Pediatric Final Rule, that there has been an increase in the number of drugs being studied for pediatric use. Only in the last few years have drugs used in children begun to undergo the same rigorous and comprehensive drug testing that has been the therapeutic standard for adults. The outcome of this law and regulation have yielded extraordinary information about proper use of drugs for children and have identified serious dosing changes that are needed for certain drugs.

Experience from drugs studied after FDAMA illustrate that such use can result in under or overdosing or that use of a drug cannot be used safely at all children. Examples of new pediatric labels with significant changes for dosing or risk include:

- Midazolam (Versed): Sedation/anxiolysis/amnesia – higher risk of serious life-threatening situations in children with congenital heart disease and pulmonary hypertension and

identified the need to begin therapy at the lower end of the dosing range in this sub-population to prevent respiratory compromise;

- Etodolac (Lodine): JRA sign/symptom relief (6 yr-16 yr) – higher dose (per kg basis) needed in younger children; approximately 2 times the lower dose recommended in adults for effective treatment;
- Gabapentin (Neurontin): - adjunctive Rx in partial seizures – higher doses required in children less than 5 years of age in order to control seizures; new adverse events (e.g. hostility and aggression) identified in children less than 12 years; and
- Propofol (Diprivan): induction and/or maintenance of anesthesia – increased mortality when used for pediatric ICU sedation over standard sedative agents (9% vs. 4%); serious bradycardia when propofol is concomitantly administered with fentanyl.

It is unethical to relax restrictions on commercial speech related to medical products in order to allow marketing and promotion of unapproved/off-label uses. The above mentioned drug are a sampling of drugs previously been used by physicians off-label because these pediatric studies were not available. Without adequate clinical trials in the pediatric population, physicians had two untenable choices for their pediatric patients: either not prescribe a potentially important therapeutic drug or use them "off-label" based on adult use and personal experience. Based on this sampling of safety and efficacy information that became available when adequate and well-controlled studies were conducted, children have been exposed to significant risks because drugs were being used off-label.

Disseminating information of unapproved uses for drugs will not improve, and will harm, the status of children as it relates to accuracy and availability of information concerning drugs for the pediatric population. The AAP expressed this concern to FDA in its 1998 comments on the proposed rule "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices (Docket # 98N-0222). Several points highlight AAP's concerns:

- Children are at an extreme disadvantage in not having adequate clinical studies performed on their drugs. With only 20-30 percent of drugs currently labeled for pediatric populations, children, and people who care for and about them, do not have the advantage of safety and efficacy studies on the vast majority of drugs.

  The adult population has safety and efficacy established in all drugs labeled for an indication for which an unapproved use is being disseminated. Expanding the use of the drug from its approved purpose (e.g., as an anti-convulsant) to use for another condition (e.g., behavioral control or heart arrhythmias) still can be based on baseline safety and efficacy information about the drug's use in adults. Children seldom have such information.

- Should marketing and promotion be allowed for unapproved (off-label) uses, the vast majority of unapproved uses for an infant, child or adolescent will not likely be based on the type of rigorous comprehensive clinical studies required by FDA for labeling purposes. Rather, the information provided to health professionals would likely be based on smaller studies that form the basis for articles that appear in peer-reviewed journals or reference publications. These are the same types of studies/articles used to "promote" the sub-optimal

or unsafe use of medications such as listed above (i.e., Midazolam, Etodolac, Propofol, and Neurontin).

- Even with current legislation and oversight, pediatricians who work with infants, children or adolescents on a regular basis are forced to rely on limited information in prescribing medications to the pediatric population. It may be argued that the risk to children is increased when a physician or other health provider not specializing in the care of children prescribes drugs to those populations. Given continuing efforts to expand the medication prescribing authority to health professionals outside physicians, the risk to the pediatric population will become even greater.

- A manufacturer who can disseminate and/or promote drug use information without doing studies in the pediatric population is significantly less likely to spend the time and resources to undertake rigorous comprehensive studies to file for labeling of that drug for children. This was clearly shown by what happened prior to enactment of FDAMA and the Pediatric Rule. According the General Accounting Office, limited data provided by the Pharmaceutical Researchers and Manufacturers of America (PhRMA) suggested pediatric study costs, ranging from under $5 million to more than $35 million. If allowed to advertise off-label uses of drugs without studies, it is a reasonable to assume that a pharmaceutical company would divert funding from pediatric studies to marketing in order to increase the sales for a particular product.

In response to the question "What are the positive and negative effects, if any, of industry's promotion of prescription drugs, biologics and/or devices?" the AAP believes that patient education regarding prescription drugs is provided best by the physician within the context of patient care and not through advertising that is designed primarily to promote the sale and consumption of a specific product. It is of concern that direct advertising of unapproved uses of medications to consumers will create an inappropriate demand for medications and/or a demand for inappropriate medications, neither of which is in the best interest of the patient.

In choosing a therapeutic agent for a particular patient's illness, a physician takes into consideration a multitude of complex factors, including the patient's diagnosis, medical history, previous medication intolerance, adverse drug reactions, possible drug interactions, chemical dependency, and the array of products that potentially may be used. Such therapeutic decisions are based on a physician's clinical experience and on objective criteria arising from a background of medical knowledge and training not possessed by the lay consumer.

Full disclosure of contraindications, warnings, precautions, drug interactions, and possible adverse effects of a drug, as required by law, without interpreting that information in the context of the individual patient's situation is potentially harmful. For example, a patient or parent may misinterpret cautionary statements that may result in undue concern and cause the patient not to take essential medication. Alternatively, a physician who enjoys the confidence of the patient and who can interpret appropriate cautionary statements can explain these same risks and place them in perspective. The latter method of providing medication information has the greatest potential for encouraging proper use of medication while preserving the patient's awareness of any inherent risks.

There is simply no substitute for adequate, well-controlled clinical trials as is currently required. A physician's best "guess" is still a guess until the studies are done. This "guessing" should come from well done, scientific studies and not be the result of a physician's uncontrolled, uninformed "experimentation" on his/her patients or the result of the "wishful thinking" of a marketing department person.

When exploring possible changes to public health protections it is essential that the historical background be the foundation from which the discussions begin. For children, the protections have been long coming and fraught with tragedy:

Historically, children have been the catalyst for legislative and regulatory protections but not the recipients of those protections until legislative and regulatory action in 1997. The legislative and regulatory protections in place today grew out of several therapeutic disasters – all of which involved infants and children. In the 1930's over 100 children died of poisoning when sulfanilamide was dissolved in diethylene glycol, a deadly poison. The chemist tested the solvent for flavor, appearance, and fragrance, but not for safety. This was the direct result of thinking that efficacy and safety of a product (sulfanilamide) would need no additional testing to be reformulated for use in children. This disaster lead to legislation requiring safety of all products.

The 1950's ushered in another pediatric therapeutic tragedy. Chloramphenicol, an antibiotic that would cure penicillan resistant infections was widely used in adults. Newborn babies with infections were also given chloramphenicol but without the benefit of pediatric studies on dosing. The results were often dire. The immature livers of infants were unable to metabolize the drug appropriately and resulted in babies turning gray and in a large number of cases, dying.

Then, in the 1960's another serious drug incident involving children lead to further legislative revisions and patient protections. Use of thalidomide, a sedative, by pregnant women caused severe deformity of their unborn children. This led to legislation that required that a drug show "substantial evidence" of efficacy and safety as a condition of approval.

Despite these tragedies involving children, the legislative responses did not extend the safety and efficacy protections to the pediatric population. It was not until enactment in the late 1990's of both legislative and a regulatory actions focusing specifically on the pediatric population that infants, children and adolescents finally were provided the therapeutic protections that were the standard of drug development for adults (1997 - Section 111 of the Food and Drug Administration Modernization Act (FDAMA – P.L. 105-115; 1998 - Final Pediatric Rule issued).

History is clear on the need to protect the public health when it comes to therapeutic drugs. President Theodore Roosevelt founded what is now the FDA in 1907 to provide protection of the public from the fraud, cost and toxicity of patent medications. In 1911, President Taft called on Congress to strengthen the role of the government by calling for legislation against false or misleading therapeutic claims saying:

"There are none so credulous as sufferers from disease. The need is urgent for legislation which will prevent the raising of hopes of speedy cures of serious ailments by misstatement of facts as to worthless mixtures on which the sick will rely while their disease progresses unchecked."

Since those words were spoken, Congress and the Executive branch have made critical advances to protect the public from harmful outcomes related to drug use. FDA must not roll back any of these essential protections.

Thank you for the opportunity to provide comments on the questions posed by the FDA on First Amendment. We strongly urge the FDA to maintain and enhance the public health protections in place, especially for infants, children and adolescents.

Sincerely,

Louis Z. Cooper, MD, FAAP
President

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These comments are endorsed and supported by the Pediatric Academic Societies.

The Pediatric Academic Societies are comprised of the Ambulatory Pediatric Association, the American Pediatric Society, the Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research. These organizations consist of pediatric researchers, full time academic and clinical faculty responsible for the training of pediatricians, and the leadership of medical school pediatric departments.